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- 6) Documents cited

 Nature 1982, 299, 178-
- B) Field of search
- 1) Applicant National Research

 By Development Corporation

 (United Kingdom),

 101 Newington

 Causeway, London

 SE1 6BU
- 4) Agent and/or Address for Service
 - R. K. Percy,
 Patent Department,
 National Research
 Development
 Corporation, 101
 Newington Causeway,
 London SE1 68U

(54) Genetic engineering

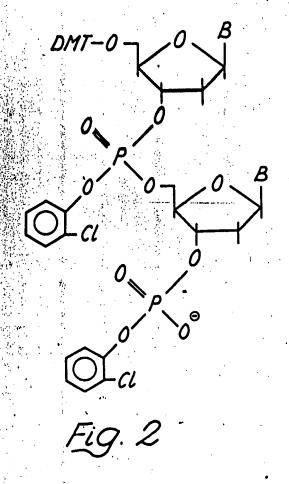
(57) It has been a problem to find an alternative, less time-consuming, and more reliable source of factor IX, a polypeptide which is essential to the human blood-clotting process and necessary for the treatment of patients with Christmas disease. In order to aid in the solution of the problem, there is provided recombinant DNA containing a DNA sequence occurring in the human factor IX genome, and includes recombinant DNA comprising substantially the whole sequence of human factor IX genome, which is

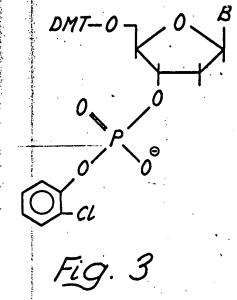
inserted in a cloning vehicle a transformed into a host, such Escherichia coli. Other fragme the sequence have also been and the invention includes DN molecules comprising part or human factor IX DNA. There is described cDNA derived from factor IX RNA. Uses include th provision of an intermediate o in the genetic engineering of a IX polypeptide precursor and t manufacture of the factor IX polypeptide, and in making pr use in diagnosing the presencnormal or abnormal factor IX ' patients with Christmas disea

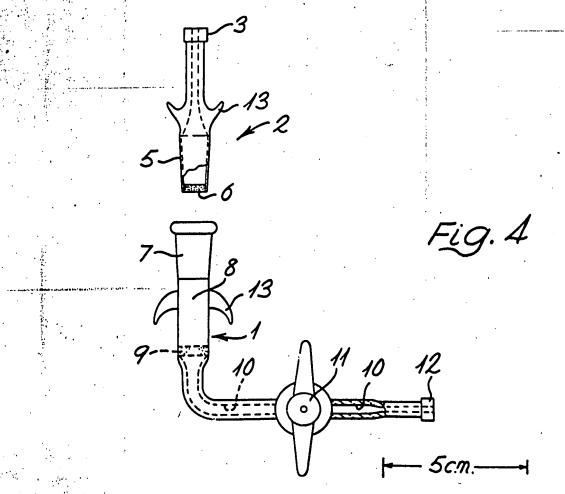
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lst amino acid		70 Glu-Cys-Trp-C	75 Sys-Gln-Ala	
mRNA :	5'	GAA UGU UGG U	IGC CAG GCN	3'
Deoxyoligonucleotides synthesized :	3 '	CTT ACG ACC A	ACG GTT CG	(oligo N2A)
	з'	CTC ACG ACC A	ACG GTC CG	(olige N2B)
2nd amino acid sequence :		348 His-Met-Phe-C	352 Cys-Ala	
mRNA :	5'	CAC AUG UUC U	JG ^U GCN	3'
Deoxyoligonucleotides synthesized:	•	GTA TAC AAA A	ACA CG	(oligo N1)

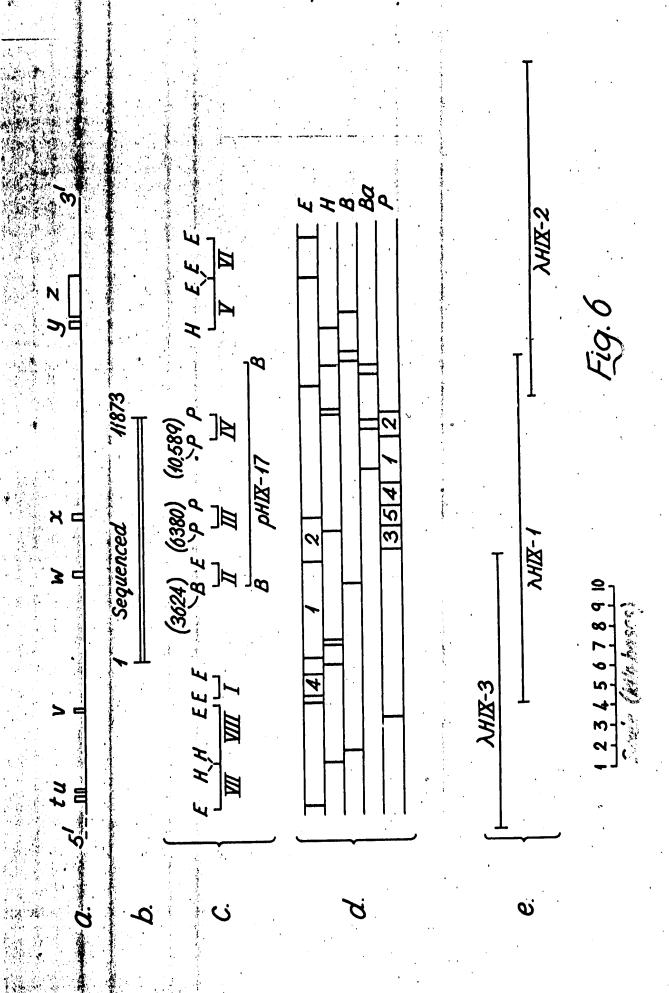
Fig. 1







SNPCLNGGMCXDDINSY TGAATCCAATCCATGTTTAAATGGCGGCATGTGCAAGGATGACATTAATTCCTAT E C W C Q A G F E G T N C E L D A **GAATGTTGGTGTCAAGC**TGGATTTGAAGGAACGAACTGTGAATTAGATGCAACATGCAGCATTAA NG CKQFCKRDTDNKVVC GAATGGCAGATGCAAGCAGTTTTGTAAAAGGGACACAGATAACAAGGTGGTTTGT 130 140 S C T D G Y R L A E D Q K S C E P A V P F P TCCTGTACTGACGGATACCGACTTGCAGAAGACCAAAAGTCCTGCGAACCAGCAGTGCCATTTCC C G R V S V S H [V R P R F H G L C S C CTGTGGACGAGTCTCTGTCTCACATGTGAGGCCCCGCTTTCACGGTCTGTGTTCGTGCTGAGAA



SAAGCTTTCA 1080	ATSAACAGG	1060 1080	CATTA(AGGGT-ATAGTAS	T TGGGT ACAG 1030	TGGATATGC 1020	ATTTCCTAGT 1610	CTC-CTCAC	GGGAATTAA 990	TTCGACTTAT 980	TCATTGGTTAGALGTTCGACTTATGGGAATTAACTC-CTCACATTTCCTAGTTTGGTTATGCTTACAGAGGGT-ATAGTA-CATTACTGCCTCA-GCATGAACAGGGAAGCTTTCA 970 980 980 1080 1000 1000 1010 1010 1020 1030 1040 1050 1050
1ATCTGTCTC 960	STCTGTCAGI 950	IGAAAGAATTT(940	46661 930	CTGAGTGGAAGA. 920	SSTTAGCCAC 910	11G-CCTCA(ATAAGTCAAA 390	CTGTCTCCA/ 880	CTTCCTAGGA 870	GATTGCTTAA Boü	TTCTJACAGCAACTGATTGCTTAACTTCCTAGGAC TGTCTCCAATAAGTCLAATTG-CCTCAGGTTAGCCACCTGAGTGGGAAGGAAGAATTTGTCTGTC
AACTACTCGT 840	SASTTATCA4 830	ATAAGAGGAT(820	846-C	agaaggaaaga 300	1 GASTGAGGC. 790	AGGAACTGA! 789	55CA A5A6 22 770	A T CC C A - GG 3 7 o 0	AACATGTGCA 750	CTTATITATT 740	AAAAAAGTCAC AAGCTTATTTAACATGGCAATCCCA-GGSSCAASAGAACTGAAGGAGGCAGAAAGGAAAGAAAG-CAATAAGAGGATGASTTATCAAACTACTCGT 730 740 810 820 830 840
TCCCCCAGA 720	710 710	16TCACTCTGT1	590	TATTCTCCAAAAC(683	. AAAAATTCA'	TTCATCACT(660	18 4 G T T T A G A 6 5 0	TAGAĞTTTAA 643	ATATGTAAAA 630	CATSTCAGCT 026	TTATTACATTTS-TCATSTCAGCTATATGTAAAATTTAAAAGTTTAAATTTCATCACTCAAAAATTCTACTAAAACCATACAGTCACTCTGTTAGCCTGTGTTCCCCCAGA 510 o26 630 700 710 720
AAGAGCCAA 600	.GTAAG-ACT 590	CCTGAAGTACC 580	174TC1 570	54TTT-CCTCCCT1 560	;-CAACAGTT(550	1161CCCT6 549	.CTGSTTCCT 530	AAGCTCAAG S20	ASCAAASGTT S10	AATTATTGGT SOJ	TCATSCCCTTASTGAATTATTGGTAGGCAAAGGTCAAGGTGSTTCCTTTGTCCCTG-CAACAGTTGATTT-CCTCCTTTATCTCCTGAAGTACCGTAAG-ACTAAGAGCCAA 490 500 500 510 520 530 540 540 600
CTTTTTG-A 480	AAGTACCAT	TTAATAGAACC 460	ATTA1	FAATTAATTA 440	AAGGCCTTT1 430	AGTGAGSAG1 420	ACCACTGTT.	CAGGAATATT 430	CAGAAAGTT 390	T AGCT AGTAA(350	TIGCAACIIIIATTAATTAATAAAATTCAGGAATATTACCACTGTTAGTGAGSAGAAAGGCCTTTTAATTAATTAATTAATTAATAAAACAAGTACCATCTTTTTG-A 370 350 360 460 470 41C 420 420 480
116C11C16 360	CTTAGCAA 350	TTGGCTGAACA 340	330	ICTACAGGTAATGT 320	. GGAACACTT1	TCATATTGAC 300	ATCACAATC 290	TTCGTAACTT 220	AGCTGCACCT	T SACA AACCA. 20 u	CATTSTECATG CCCT SALA AGC TGC AGC TTTC TATC ACATC TCATATTGAC GGAAC ACTTTCTACAGG TAATGTTTAGCTTGG CTGAACACTTTAGCAATTGCTTCTG 250 270 270 360 360 360 360 360 360 360
ATTCATTCC 249	ACASAGTTT 230	ATTGAGAAAC 220	TCACA 210	CAATGACACAGAA 200	ACTTCTTAGG 190	465TCT66TT 180	ATGATACAG	ABTRTSGASA 1e0	45-66TG4C4	T 64 5C CC TAA.	CAGCAGCAACATACTGAGCCCTAAAS-GGTGACAAAT\$TSGASAATGATACAGAGGTCTGGTTACTTCTTAGCCAATGACAAGAATTGAGAAAACACAGAGTTTATTCATTC
GATCAACAG 120	CAASCCAAA 110	CCTGCGCAAAA 100	CACCT 90	AAGCAATATTTCC 30	6CTGAT136 70	SCAAAAGATT 60	TAGCTGA3G(Sû	TTCASCCTTT +0	11C16GAATC 30	ATTATTTATI 2C	GALTICCTIGICCATLITITATITCIGGAATCTICASCCTTITAGCIGASGGCAAAGATTGCIGAAAGCAATATITCCCACCICCIGGCAAAACAAGGCAAAGATCAACAG 10 10 20 20 100 100 20 100 110 110 120 12

FIG. 7a

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2270	2390	. TCT 6	7ABGTA.	2750	ACGTT	. 2970	67CCC 299	161 AČ 311	AGCAC 323	AGTATG/ 3350	
2.	CATT	CTAGET	AAAA	ATATC.	A T C A G		CAAAS	AAACT O	GAAGA	CATGA 0	
2265	TATGAACCACA 2380	TTAAACAGT	TGAAA.	74CAA41 2740	AAATT.	2860	AATAC	AGAAT 310	SCTCA 322	14TGGC 3340	
7. 2. 4.	ATATG	CTTA4	TTCAC	51CAACATACAAA 730 2740	ATAAAI	·	AATGC.	GAGGA	AGAGT(ATTCA 0	•
2250 2250	.GGTATA 2370	TAACCT	2510	46 A G T C / 2 7 3 0	TCTAC	2850	6ATTC	309	ACACT.	TAGATA'	
5	TCCAT	ATAGGTA		GATAC	AGAAC	6	TAATG	AGACA.	GAAAC O	TCAAT 0	
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פריים ביי	CTGCA	TTCTA	GTATCTACATGAGATTATSAAATTGCGGTTGCTT 2530 2590 2600	AAGAT O	CTTASTAATAAAT GTGAGAAAGATGTSCAAGAACTCTACATAAAAAATTAT	o.	AAATG	A TGGAAATGCAAAGACCAAGGATAGCCAAGACTTTTGAGGAAGAATAAACTTGTACT	ATAGA O	AAGTG	
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788CAC:1		SACTT	TGAG	AATAAG 1 700	AAAT (0.	TAAA	CAAA(A56AT	GTTTTC/ 300	
CTYBA 222	2340	CTAAA	CTACAT(2530	27C	.ST&A1	282	ATATAC 294	304 30¢	ACACAL 31	166761 330	•
A A G T T	A A TCTCC	4				2	TA CA	⊢ 0		: -	•
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, TG TS	C 4 4 4 9	CTAAC	IGCAG4	ATCT.		· 6	ATCAATT 2920	TATAA 40	4464C46 3160	AGAGA 30.	
C * TCT Y 1	7 CCC 4 C / 23 2 0	C T A T 1	7TC4ATG(2560	. A & A G C 41 26 3 C	5C & TT,	2809	TT T TT 29.	CTAAT	AT TAB	5C AGT 32	
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7CC 46747 2180	CTCCASC 2300	6115A 20	AGCAATA 2>6G	TST 4C4T	216AT	2786	TABATSA 2900	66646 26	TATC6	GATAG GO	
SACTCI 21	46CCT(11126	CT 44 G	GATTS 20	ब्षम ए 🤉		29 - 29	30158 30	CT TAT	1TT TAT 32	
CCTCCCTCAAGTASACTCCAGTATCTGTTTGCTTTCCTTGTGTTTATA 2170 2170 2210	TCCTAEGSATGATEGCCTCCAGCTCCATTCCCACAAAGACATA 2230 2330 2313 2320 2330	TCATTGATGGGCATTTAGGTTSATTCCATGTCTGCTATTCTAACACT	ATTICTAGAATAACTAAGCAATAGAAATTACACTTCAATGCAGAAAGGCA 2539 2540 2550 2560	TTTCAGAAAAATGATTSTACATATAGAAAACCCAAAGCATCTAAACAAT 2650 2000 2670 2680 2090	ac c a sca acca t te a a batga t t t t t a t a a t a g c a t t m a a a a t t a s a c s	2773	TTAAGGAAAACCTAALTAAATGAATAGGCAATGTT TATCAATTAAAGGA 2990 2990 2990	TTT GGTGGTGG 346 TC GGGCAGGATTCATAAGCT AATTATAAAATGCA 3010 3026 3030 3040	CCAGATGTCAAGACTTATCGAGTTACATTTATTAAGACAGTGTGGTA 3130 3140 3150 3160	TAT A4AGGCTTSATTTATGATAGAGGTGCCAGTGC AGTAGAGAAGGAAAT 3250 3290	
CCCTC 21	TAEGS 22	TT6AT	TCT 46	CAGAA 26	4.5.C.4.	27	A66A4	365166	164T61 31	7 A 4 A G G	
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4 90	17 A G A 3 6 9 0	ATTA 3720	5 A A C T 38 4 0	CTGT 3960	SATTGGGAGGGGGCATCTTCTGGGGTATTGATGTGCTATTGGTCAGTTTAGTGTTTAAACAGGC 3 4020 4030 4030 4040 4050 4060 4070 4080	FATATGITATACATI AATAAATAGGGTTTTTAAACCTGTAGTTCATAATTTAGTGAAAGTAGAATATCCAAA 30 4140 4150 4160 4170 4180	657A 6320	4440	CTCT 4560
45 TGATCACCATAA ASGAAAAGATTGATAAACTGGACTATATTAAAACTAAGGACTCCTGTTCAGCAAAAG		ACACTCATAAÎTAT AAGCU, GTAAAAAGGCATGTTTATGTCACCAAAAGATATATACAAGAATGTTCATT 0 3560 3670 3680 3680 3590 3700 3700	AACAGTAGAATGAATAAATAAAGCTGTAATAGTAATACAGTGGAATACTACAGCAATGTAAATGAAC 0 3780 3830 3840	TTACTG 396	AACI	ATC	CAA	101	5101
TCAG	TCAT	ATG	TAA	131	TTA	AAT	. 55	1667	24 C C A A A A A A A A A A A A A A A A A
16T	46 A T C A T T 1 3 5 9 0	1AGA 5710	1 A T G	3 4 5 C	5161 6070	61 A G	CTC1	4430	N D 12CCAG
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11A	00		.TG6	ATT.))	TTCA	CAA	SATG	ATA1
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1040	TGA	TTA	AAT	611	101	5 T G		5 T T A	T GA
CTC	C A C		AGT	111	ATAA O	A A A C	CAC	CATO	C T C
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T G A	222	AAA	5 T 5	ອວອ	. G T A	5611	777	4 5 A A	1501
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24.00 27.00	A 4 0	A C A		. A A D	SAT	FATA SO	50	A 50	A O O O
341	70 TG 353	355	1CCA TT/ 377	44 A T 3 3 9	6 A A T 4 0 1	6 A A T	15C4	ATG.	* 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4
T & C &	ATA	A GT	A TC	G T T	6 TG	111	.T.T.&	I T AC	C 11 51
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340	A 6.4 C	5 TG 4 364	ACC 4	36.5	40.0	161	ATC.	1 GA	77 305 305
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TAA	CT S	461	TÀA	וְאַמְּרָ	1 Ge T	3 T S &	A SA C	ACAT	n T A A C
77 C A	4 9 D	13 13	TA C. A 39	ACA 3 5:0	7CC 4	, 1119 90	ر 11 <u>11</u> 10	SCA i	C 376
AT 11 337	ACT1 345	SC 11	11A 1	T6T.	A A S	1AC 4.3	461	0 9 5 0 5 0 5	7 T
AATTTATATTCATAACTTGCAGAA4GCAAAAATTTCTTAAAATACAAAA 3370 3360 3360 3340	ACACTACTTCGACTGAAAAGACAAAGTCACAGAGTGAGAGATATCTGAAAAGACAAGATATCTGAAAAGACAAAGACAAGAGAGAG	ABATTGCTTGGCAGTAATCTAGATCTGAACATGTGATCCAGTAATT 3010 3620 3530 3640 355	Cactattatacataa sa gccaaaaactsgaa acaa accaaata tccatt 3730 3740 3750 3760	ACT GCT GT ACA CALGGTTTAATCT CAGAGAAAATGTTAAA1 3850 3860 3870 3880 383	GTTASAAGTCCAGUTAATGGTAACCTATAAAAAGGAAAAAGGGTGGAAT 3970 3960 3990 4000	TCATTTACTTTSTGE AAACTTECACTAAAATTGTGTGTTTTTTTTGAAT 4330 4100 4110 4120	CATITAGITITAAACCAATCAATTATAGIGCIACCAICATITITAIGCATAATGASAAGITI ATITITACCITICIACTCTTATITCAAGGCICCAAAATTICICICCCAACGI 4210 4220 4230 4230 4230 4240 4260 4260 4270 4280 4290 4290	TATISGGGGGAACATGAATGCCCCCCAATGATTTGACCCCATACATGAGTGCATGTTTTAGAAATGCATGTTAAATGATGCTGTTACTGTCTATTTTGCTTCTTTT 4350 4340 4350 4350 4350 4370 4380 4380 4390	POVT C N I N S R C E G F C K N S A D N K V V C S C T E G Y R L A E N Q K S C 1 C N I N S R C GATGTGCTGAGGGATATGAGAAAGAAGAAGAAGAGTGCTG GATGTGAAAAAAAAAA
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FIG. 7e

4589	4800	4920		1CAGC 5160	7 GA T 5 2 8 0	5400	3520 5520	5640	16667 5750
GAACCAGCAGETTTTTAAAGATTTTTTAAAGAAATCTGTATCTGAAACTTCAGCATTTTAACAAACCTACATAATTTTAATTCCTACTTGAATCTGCTTCCTTTTGAAATC 45701 4580 4590 4600 4600 4610 4620 4630 4680	TAGAAAATATCAGTAGCTTGAATTAGATTAGATTGCATCATATATTTAAATATAAAL ATGTAATCATCTGCAATTCTTGAGTCCAATTTGTCCAATTTT 4620 4700 4710 4720 4730 4740 4750 4760 4770 1 4780 4790 4800	TTTCTCTALCATTTATCACAAGCAATTAATTTGTGTTTTCTGCATATGTAATTCATCAAGTCAATGTAGTAGTATACTATATCATAAATATACAAATAATTGA 4810 4820 4830 4840 4350 4860. 4870 4880 4890 4900 4900	GTGATAGGCTTCTAGTATAGGACGGTAAGTTTGAAGCATGATTCTATCTSGCTGGCTAGTTTACTCTGGGAAAGTTATTTTTTTTTT	GTC ASAATSATTCCG GC AA TG AACTGTTTTATGCTAGG CTGA TCASCACAATCTATAT GGCTGTGAACAAACAATGTTTCCCAGTCATACCAACCATGCCACCATTTTAACAGC SOSO SOSO SOSO SOSO SOSO SOSO SOSO SIOO SIOO SILO SIZO SI3O SI4O SIASO SIASO	TGATTAGTSTATTCAGAACATCTCCACTCCATGTTCGTATGSCTGTTATCTAAAGGAGGAGGACACTTTTATTTTTGAAAATTTAGGCTCTGCAGGGTCAATTATTTTGAT 5170 5186 5180 5180 5200 5270 5220 5230 5280	4aa igaggggc tiitti baagcaaactagatataa tiictitigcatiitci maggceigatatettaatiiggtacattaaatigtgcaccattictcigtaact 5290 5390 5300 5310 5320 5330 5340 5350 5360 5360 5360 5370 5390 5390 5400	TCT CAGCACTATACCAGACAAAAAAAAAAAAAAAAAAAA	GASTATGAAGTGSGAJATCAGGGSTCTCACAGCCTTCAGAGCCCCGGAACAGAGAÎTTACCCACATATTTATTGACAGCCAGTCATAAGATTTACTGAAAGTATTCCTTA 5530 5540 5540 5620 5530 5570 5580 5590 5600 5610 5620 5630	TGGGAAATAAAGGGATGAGTGGTGGTTATCTGCAGGAAGATGTCCTTAAGGAATGATTGTCTGTGGTTTAAGAACACCTTTAAGCAGTTTTCCGCCCTGGGT 5650 566 567 5670 5630 5750 5750
TACTTGAATCTG	10 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	ATATCATAAAAT 4900	66TCTTA46CTC 5020	ATACCAACCATG S149	AGGCTCTGCAGG S260	.CATTTCTCTGT4 5380	GAATTAAAGAC	STCATAAGATTT	ACACCTTTAAGC 5740
ATTTTAATTCC 4650	ACAACCTGAAT 4770	GTAGTAATACT 4990	TTTTATTGTTG 5010	GTTTCCCAGTC 5130	TTGAAAATTT S250	AAATTGTGCAC S370	CGGCACTAGAG S490	CAGCAAGCCAG So10	.TGGTTTAAGA4
AAACCTACATA 4640	TGTAATCATCT 4760	GTCAAATCAAT 4980	AGAAAGTTATT SOOO	AACAAAACAAT S120	ACTTTTATTTT 5240	ATTGGTACATT 5350	CCCTAATCCTG 5480	ATATTTATTGA 5600	GCAATTGTCTG
AGCATTTTAAC	BATATABAL A	TABTTCATCAB D. 4870	AGTTTACTCTG 0 4990	ATAT GGCTGTG 0 5110	AAGC AGTAGAC O S230	ATATCTTATTA O 5350	66TC AGGGAGA 0 5470	GAÎT TACCCAC O SS93	AAAT CACTTAT 9 S710
TCTGAAACTTC	ATCATATTTA	ATATGTATȚTG Sû 4861	CT556CT56CT 7098	CASCACAATCT 90 S10	TCTAAAGATGA 10 522	TCT = AAGCCTG 30 534	GAGATCAGCTT SO, S&6	CCCCGAACAGA 70 SS8	CCTTAASGCAC 90 S70
SAAATCTGTA 600 40	TTCTAGATTGC 720 47	6T5ATTTCT6C 840 43	CATSATTCTAT	GCTAGGCTGAT OBO	TATGGCTGTTA 230	10111160411 320 53	GAACCAGTGCC	AGAGCTGAGAG Seo SS	CAGGAACATGT 630 SS
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FATCTGAATA	AGCTTGAATTAG 4700	ATATCACAAAG(4820	6 TA TA A G S A C G C	GGC AA TGAACT(SOGO	AGAACATCTCC 5180	TTT baaggaaa(5300	C 4G G C A G A A G A S A S A S A S A S A S A S A	A 3A TC AGGGGT 5 S4 C	ATGAGTCSGCT Soéu
GAACCAGCASS TCA 4 5 7 9	GAAAATATCAGT 4690	TCTCTAACATTT 4810	GATAGGCTTCTA	CASAATSATTCC SOSO	ATTAGTSTATTC 517D	A T 5 A 5 G G 5 C T T T 5 2 4 3	T CAGCACTA T 2C 5 4 10	15 TAT GAAGT G5G 5 5 30	GGABATABAGG SSSD
5	4	Ħ	5	5	. 2	F.	5	QA .	12

6489 6489 6600	6470 ATTATATTAG 6590	6460 6460 6580 6580	6450 6450 676447476	TCTTCZTSATACTTTSTCSCESCTSGTTGCTATAGAMATSTCTGTTACAAGGAAAGGAAAAGGAAAAGGAAAATGGTGGGGGGGG	5430 5430 1848416G16G	5420 5420 5420 5420	57 TACAA6.5A6 6410 6410 54 AAA AAAA AAC	0400 0400 111111111	6390 6390 Caatacatta 0510	6383 6383 50008515181
646116016 6360 64447700	6350 6350 6350 6351 631113861	AAGTGACTT	ISAAATGTG	TC T TC A TA SATA SITISTES CASA TO TO TO TA CAAS GAAT G T G G G C T G AAG G A A G T G A A A A T G A G A G	. A G G A A G T G A	.16166C1164	STTACAAGGAL	15 a matstet	1667166131	TTSTCGCBSC
56CCAAAC 6240	GAATAAGTA 6230	ATTTCCTGT 6340	TTGAACTA	ACATAASTÄTI 6320	GTACACTTAT 6310	16116A1161 6300	1C 1G 1AG C CA 1 6 29 û	16 GTCCCTTT'	TTA AAGT TTT CTGCCTTTT CAATGATAAGGTCCCTTTTCTGTA 0250 6270 6270 6299	TTCTGCCTTT 6265
36CATACT 6120		46CTTT46CA 6223 4TTTCTTT 6340	ATAGCCTT 6210 11GAACTA 6330	AGAACCACCTCCAACTATTAAGTGTTATATTTGAATAAGCCTTAGCTTTAGCAGAATAAGTAGGCCAAAC 10 6190 6200 6210 6220 6230 6240 10 6300 6310 6320 6330 6340 6350 6350	TATTAAGTGT 6190 GTACACTTAT 631G	CACCTCCAAC 6180 15150 16116A1161	.aattgagaaC 6170 10761aCCa1 6290	A GAGAAA CAG 0100 16 GTC CCTTT 15	TATGCTATAB 6150 TCALTGATAB 6270	CAAGTTCTTC 0145 11CTGCCTTT 0200
6000 6000	TAGACAGAT(ACTTCCASTA 6103 AGCTTTAGCA 6223 ATTTCCTGT	AAAACCTA66090 ATAGCCTT66210 6210 ATGAACTA6330	CIT CACGITACA CTUTICAAAGCTASTCTACCTTG AGAGGGGC ATGAATATGTGTGTGGGGTGTGTGTGTGTGTGTGTGTGT	6070 6070 1ATTAAGTGT 6190 GTACACTTAT	1616661616 0050 CACCTCCAAC 0180 16116A1161	TGAATATGTG 6950 ;aattgagaaC 6170 rctgtagcca1	6 4 6 4 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6	FASTCTACCTT 6030 TATGCTATAW 6150 TCAATGATAA	JUTCAAAGC 5520 CAAGTTCTTC 0145 TTCTGCCTTT
	TGTTCTTCTG S990 TAGACAGATO	CTGCCCACT 5980 CTTCCASTA 0103 AGCTTTAGCA 0223 ATTTCCTGT	6090 5970 6090 6090 610 6210 6330	GITTATGGCCASATTIGGASGCCTGTTCCCAACAAACCAGGAATATATCCTGCAAATAGAATCTCTAAGGCTTCGGGCCTGCCCCCTTGTTCTTCTCTGCCTGGTTC 5500 5500 5500 5000 5500 5000 5500 5000 5000 5000 5000 5000 5000 60	SPSD SPSD IGTCTGTGTA' 6070 TATTAGTGT 6190 GTACACTTAT	FATCCTGCA & S	TAGGAATATA 5930 TGAATATGTG 6050 SAATTGAGAAC 6170	A A C C A G A A G C A G A G A G A G A G	IGTTCCCAACA S910 FASTCTACCTT 6939 TATGCTATAA 6150	TTGGASGCC1 5900 JTLTCAAAGC 9520 CAAGTTCTTC 0146 1145 6260

1146CH2616TGT 2010 8020 8030 8040	80 80	0008	DC B BBB	7 9 7 0 0 0 0 7 0 0 0 0 0 0 0 0 0 0 0 0	.CG A A CC CC A C C T C 79 6 D	.GG-CAACACG- 7950	TAACCGa-atttga-aac-cctgg-caacacg-cgaaccccactt 7930 7930 7940 7980 7980
7900 7910 7920	7890 79	7880	0	7850 786	0762	.6TTCTC6T 7830	AGA GTCT TGA TCTAC CACT ATA GTTCT CGT — 7810 7820 7830 _
	36CAAGAACTAGG 7770 77	56a66aa66a ji taa 7750	AAAGGACTCAA 0 7750	4 4 4 5 G G G G T 7 7 3 0	AT TGGATTAT TTA 7720	66CT 4A6A AAA 7719	GGT GAGAGTTG GAAGTCTTTAGGCTAAGAAAATTGGATTATTTA 7500 7710 7720
CATSAASSTCTGSAAGAAAGGTCGCAGTACTCAGGCTTCAGGCTTCAGCCTTGCAAAACT 7610 7620 7620 7680 7680 7680	AGGGCACTACTTC 7650 76	AGGTACTCAGGTTC. 7640	A A G A A A G G T C G C I	CATSAASSTCTGS/ 7610 7620	465TCAACAA 7600	TCCAGACAGSC 7590	TAAGGAAACAG CATA GCAG GATTC CAGACAGGCAGGTCAACAAG
CCTC CAGAGATGAGCA GTTGGTGAAAGAGGGCTCAAAACCAGCTACCATACAGGTCAAGAAGAATTTGGCAT 490 7500 7510 7520 7530 7540 7550 7560	ACCAGCTACCATA(7530 754	1agagaggetcaaa1 7520	15CA 6TTGGTGA4) 7510	GCCTCCAGAGATG1 7490 7500	CC ÅATGTGAGAAG 7430	TTCAGCACTAA 7470	TGT GASA & GTATTTA SGCA AGTTTCA GCACTA ACC À ATGTGAGAAGG 7450 7450 7460 7470
AACTGGAGCTCAGCTGGCCAGGTGGGAGACTGAGGCTATTTTACTAGACAGAC	.ACTGAGGCTATT1 7410 74:	AGGCCAGGTGGGAC 7400	SCTGGCAAGACAC		16 A 16 5 1 6 1 6 1 6 4 5 7 5 0 0	GTACTTTATAC 7350	P G 2 E P m Q ACCAGGCAATTCCCTTSGCAGFACTTTATACTGATGGTGTGTCTAA 7330 7340 7350 7350 7360 7
N I F Q S F Q S F N D F T R V V G G E D A K ACATCACTCAAAGCACCCAATCATTTAATGACTTCACTCGGTTGTTGSTGGAGGAGGATGCCAA 7260 7270 7280 7290 7300 7310 7320	D F T R V. ACTTCACTCGGG1 7290 730	G S F N CCATCATTTAATG 7280	T Q S T CACTCAAAGCAC	I L D TTTT:GATA 250	E A E T IGAAGCTGAAACCA 7240	V N S T STABATTCTACT 7230	V E P D V D Y V N S T E A E T IGTITITCCTGATGTSGACTATGTAAATTCTACTGAAGCTGAAACCA 7210 722G 7230 7240 7
Q T S K L T R A E A A A A A A A A A A A A A A A A A	7 S 117 C A C 717 O	V P F P C G R V S TITCTAGTGCCATTCCATGTGCAGAGTTTCTG	P F P C GCCATTCCATG 7150	130	ACTAATTTTCT1	18ATATCAGGT1 7119	ACATSTICCATTIGC CAATSASABATATCAGGTTACTAATTITTCTT 7090 7100 7110
SCTTCTCAGAAGTGACAAGGATGGGCCTCAATCTCAATTTTTGTAAT. 7040 7050 7050 7050	gacaaggatgggc 7050 700	SCTTCTCAGAAGT > 7040	, aaatac tgatgggcc 920 7030	10 010	CTATTCACTGATT 7000	ASCTTGAGACT 0990	SAAAATAACSCAATCAACCTTTTASCTTGAGACTCTATTCACTGATT
GICATTAGACTCT3TAAAAGTCTTACCAAATTTGAATCTGCTATTTCCGTAAAGATGATGAATTCCGGAGCCAAATGTTCTTTTCATGAAGGATTTGAAAACTGTCCAT 61CATTAGACTCT3TAAAAGTCTTACCAAATTTGAATCTGTTTTCTATTTCCGTAAAGATGATGAATGTTCTTTTCATGAAGGATTTGAAAACTGTCCAT 6950 630 630 630 6870 8830 6890 8900 6910 6910	TGTTCTTTCATG 6930 694	ATTCCGGAGCCAAATGTTCT 5920 6930	TAA AGATGATGA 0910	TATTCTATTTCCG 290 5900	ATTCTGGBACACC 5830 6	TACCAAATTTG 0870	GTC ATTAGACT CT3T ABAAGTCTTACCAAA

TTATAACTCATAAATG 9230 9240 FIG. 7h	CTTATAACT	9210 9210 9210	GACAATATT1	9200 9200	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	9000	9050	9040	9030	9020 9140	9130
0006	0668	0868	8970	8960	8950	0768	8.930	8920	8 1 C 8 1 C	8400	00 00 00 00 00 00
	8870	8660	8850	0788	8830	3820	ສາ ວາ	0046	8760	8780	8770
8760	8750	8740	8730	-CCT>TGCC&C&A>C&TC&TC&TC&TC&TC&TC&TC&TC&TC&TC&TC&TC&T	76CCACAA61 8710 	3700 3700	31 A A C T T A A B A C T 3 A 9 O	3680	ACCACTTATAS E670	TTC TATT CG AT 800 C.	TACTGCAGAAATITCTAITUGATAGCTTATAATAGTTTAGTGTAA
ACTCTAT 8640	AGATAGAAC 8630	TTAAGCACATAACAAC CACATGTGG-TAGTAACTACTGTATTGGAGAGGCGGAGATAGAACACTCTA 570 8530 8590 8640 8610 8620 8630 864	767A776GA(8610	7AGTAACTAC 8600	CACATGTGG- 8590	ACATAACAAC 8530		.C.A.C.C.T.G.C.C.A.A 95.60	TTC-TCAATTG 8550	AAAATTCAA 8540	ATTANGAGAAATTAAAAATTCAATTG-TCAATTGCACCTGCCAAATT SS30 8550 8560 8
ATTAACTACA 8520	ATTTAAATT 8513	GTCCTTATAAAGTT GTGCTGT-CAATAGGTAACCACTAGGCACATATGTTTAAATTTAA/ 45G 346D 8470 8480 8490 8500 8510	ACTASCCAC! 8490	ATAGGTAACC 8480	5TGCTGT-CA 8470	TATAAAGTT (3460	A TG G T C C T T 4 8 4 5 G	6 raa GCC a G S 2440	CTCCCCAGGCA 8430	7 166CCCCC	AAT AACCCACCTCTTTGGCCCCCCTCCCAGGCAGGAAAGCCAGSATS
6A5AA6A 9400	6390 8390	CTACATTTGTAGCAAA ATCTGGGTTGTAACTTAGCCTACAGCTGAAGCGTAAGAGATTCGGTGAGAAGA 330 8340 8350 8360 8370 8390 8390	TACAGCTGA/ 8370	TAACTTAGCC' 8360	8350 8350	TGT AGC AAA 6 8340	G-GCTACATT · 8333	TAGCAACCAA 932û	. ATTTTTCATT 8*10	ACCTATGCAC 830C	5 ACATATGTAGAATTACCTATGCACATTTTTCATTTAACAACCAAG-6 8290 8300 8310 9320 8
AACAACCT 8290	TCTGCA 8270	TCTCCAAGCGTAG 8260	TGCASACAT1 8250	AATAATGCACTTGTAC CTASTCCTTCC CGGTGCTCTGCAGACA 210 8250 8250	3230 3230	CACTTGTACC 9220	CCAAATAATG 5210	GTTCAAAACA 3200	agaagees; aton	2 ACTTGTTAG 818 Ū	SCCCHAAGGAAATSAACTTGTTACAGAAGCCGGGGTTCAAAACACA 8170 8180 8190 8200 8
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			电电路电路 医电影 经基础证明			Strange Control of the			- Ay		The state of the s
14C ACT 6 8160	AAAGAAA 8150	ATCACACCACTGCACTTCAGCCTGAGTGAGAGCCCTATCTCAAAAACAGAAAAAAAA	AAGACCCTATC 9130	GACAGAGTAA 8120	CAGCCTGAGT 3110	CACTGCACT TO 8100		CAGTGAATTC 4085	AGCCTĞSAAAGTCGAGGCTGCAGTGAATTGT	GAGCCTGSAA 8GoO	TG GAGAATCA CCTGAGCCTGSAAAGTCGAGGCTG CAGTGAATTGTG

	111GIC 9480	644C46 9600	₽CCCC6 9720	16AGCC 9840	6TTT 9960		10080	10200	10320	
	**************************************	GTGGGACATA 9590	ACATAGTGAA 9710	GAGCTGGCAG 9830	761-11616A 9950		10070	10190	TGAAAGACCC 10310	FIG. 7i
	11GTATCTAT	9580	ATCCTGGCTA 9700		44465161- 9043	•	10050	10180	AGAATAGTTS 10300	
The Control of the State of the	FTTAATATCC! 9450	GGATAACATGGTTACAACAAAGATCCTACTTTATGACAATTATCTTCCTTGGGTTTGTGGGACATAGAACAG 530 9540 9590 9560 9560	AAGATAACTTCCGTTTTTAAAAGTCCAAGATTCAGGAGATCAAAACCATCCTGGCTAACATAGTGAAACCCCG osu 9660 9670 9680 9690 9700 9710 9720	TATA GTCCCAGCTACA CGGGAGGCTGAGGCAGGAGATGGCGTGAACCGGGGAGGCGGAGCTGGCAGTGAGCC	aaaaaaaaaaaaaaaagtCCaaGTTTaaaaaaaaaaaaaaagagTGT-TGT-TTGTGAGTTT 690 9920 9920 9910 9920 9930 9940 9960		10050	10170	NITCAAAGCACTITATCTTTCCAAAGGCAAGAAGCTGAGCTACTTTCCAGAATAGTTSTGAAAGACCCTGTCAT 1250 10260 10270 10280 10290 10300 10310 10320	
	CTTCAATSTA1 9440	FACTTTATGA(9560 ;	AGATTCAGGA(9680	66CAGGASAA 9800	AAGTTTAAAA 9920		10060	10160	AAGAAGCTGA 10289	
0104	5TTATTATGC(9430	CAAAGATCC: 9550	TAAAAGTCCA. 9670	666465C76A	AAAAAGTCC 9910		10030	10150	TTCCAAAGGC 10270	
	GCAGCACTO 942D	15GTTACA A(9660	CAGCTACAC 9780	18888888888888888888888888888888888888	6	10020	10140	CACTTTATCT 19260	
	CCTCTTAAG1 9~10	ATGGAT 44C4 9530	45446A TA3(905U	,CC TATA GTC(9770			10010	10130	10250	
C.07A	TGGAACAATC 9400	TCCAACTTCC 95.20	atattascta 3643	5755CA5GCG 9760	AGCGAGACTC 9830		10000	10120	TGATSTGAC: 10240	,
CONTRACTOR DESCRIPTION OF THE PROPERTY OF THE	SAACCTTIFC 9390	7C3T7ATGTG 7510	CCAGSAGAAT 9630	6CCC5GCGTG 9753	7655C64CAG 9873	·	0666	10110	CCCTATTCAACCACATGAACAGATTACTGATGTGACAGA 19219 10220 10230 19249 10	•
207	CCTTCTTTA-' 938C	61 A T T T T C A T	ATCCAASAAC 9326	Cababatte 0746	CACTCCAGCC 930G		0866	10100	CAACCACATG 10220	.:
	ACTECTSTAATATTGACETTETTA-SAACETTTECTGGAACAATCECTETTAAGTGCACTGTTATTATGCETTCAATGTATTCCATGTATCTATTECTCTAATTTTGTC	ATTITGIGITCICATGIATITICATTCATTATGIGICCAACTTCCAT 94.40 95.00 95.00	TGC TCAGAGTASSGGATCCAASAACCCAGSASAATATATTASCTAAS 9512 9510 9526 9633	TCTCTTCCJAAAATTAGCCCGGCGTGSTGGCGGCGCCCCCGCCCCCGCCCCCCCCC	GASATCCCSCCACTGCACTCCAGCCTGSSCGACAGAGGGCTCC- 9850 9870 9380 9870		0.20	100%	CCC TATT 10210	
	ACTCT	ATTT	71 291	16.1.6.1	GASAT					

10460	10560	10680	10900	166ACT	11040	.GGCTAA 11160	11280	11400	11520
10:30	GCAGCAAACC 10550	AAAGAGTGTT 10670	CATAGAGAGT 10790	AACTTCTTTG 10910	GAGCAAATGT 11030	GATCAGAGCA	TCACCTCAGO 11270	CTAAAGCCAA	GCGCGATGGG 11510
10110100 11 10110 11 11 11 11 11 11 11 1	AGATCAGACT 10540	GTCACCTAGA 10600	CAAAGAAGAA 10783	AGGGGAGGAC 10900	AASAAA SCCCTTTCCAACCAACCACTGGTTGGTTACACAGGTTGGGCAGCATTGGGAGCAAATGTTGATTG 13970 10980 10990 11000 11040	11140	TCCAGGCTT 11260	TTGCTACCTC 11380	CTCCAGGCCC 11500
04444741054 10410 - 4	3ATTTGATTGC 10530	IGTTTAGCAGT 10650	AAGAAATCTCA 10770	CCACAAGGGA4 10890	ACACAGGTTGG 11010	GCATTTGTTC4 11130	TCTTACCTTA1 11250	-CCCATCCTG1	CTTCAGTTTC(11490
1000	SGAATACTA(10520	TATGAAATAC 10640	10760 10760	TTTGCAAGAG 10880	11000	CAGGGAG-GG	CACGGTCATT 11240	ACGCCCTG- 11360	GAAGGAGSTA 11480
10390 - 10390	TCTGCAGGSA(10510	TAGCTTTG · A 10030	AATAAAGTGA 10750	AGGTGAĞCTG 10870	CAACAACCAC 1099D	TAGCCCCATT	11230	TGGTTCCGGA 11350	GAGGCCAATG
370 - 27-10390 10390 - 370 - 27-10390	10500 10500	ATTATATATC 10620	CAG3GTGGGA 10740	GAAAAGGTGT 10860	CCTTTCCAAC 10980	AGCGGCTAGA 11100	GCACGTATCC 11220	6AGCCCCCTA 11340	66AAC6GCGT 11460
4 10370 **	CTCCACCA TG 10490	TGGTGAAAC. 1051u	CAAATTTAGC 10730	GTCTGTTAAA 10350	TTAASAAA SC 13970	6ACT 5656 AC	TGTTCTCCTA 11210	AGCTTCCCAG 11330	GTTCCGGACA 11450
	54 TGGCCAG 104 80	56 56CT TCAG 10603	TTTTATCTTT 10720	GALATGSTTA 10840	CT 54CCTCCA 10960	6C * GTTCTGT 11080	TACAGASCCA 11200	TCGCGATGGT 11320	AGGTTAGAAG 11440
103507774 103507774	CTCATTTGTG 10470	AGCAACASCT. 10590	SAGTTGTTTC 10710	GAACAGACTA	CAAGACGATTO 10950	SACTTABASA 11070	TTTGAGACCC 1119C	CCGC-CTTGT 11310	AAGTCGCGCA 11439
10340	AG AATCTCTCI 1046C	AG AG AA AG CA 10530	111C1C11CA-	TGAACAGATTO 1002 G	TGCAAGCAGG(CGGAATTGTT	CC 16 TC C 4 S C 11183	65 CAACGCAG	.CCT TCT A 11420
ALTICICATION 1010 CONTROL TO A	AAT GAAAGAAACCAGAATCICTCCTCATTTGTGGATGGGCCAGCTCCATGTCATGT	SACTANGGCATCANGAGANGCANGCANCAGCTGGGGGGTTGANANGATATTATATATTG ATATGANATACTGTTTNGCAGTGTCACCTAGANANGAGTGTTTCANA 10570 10530 10590 10600 10600 10610 10620 10620 10630 10640 10650 10650 10660	TWCTGATSCAACCTTTCTCTTCAGACATACTTTCAAATTTCAGGGGGGGG	TCATCTGGAGTAATGAACAGATTGAACAATGGTTAGTCTTAAAGAAAG	TAAGSGTSAAAGTTGCAAGCAGGCAAGACGATTCTGACCTCCATTAA 13933 1046 10945	AAC LADIGITTS ICGGAATTGITGACTIAD ABAGC 76TTCTGFC ACT 3656 ACDGCGCTAGA TAGCCCCATTCAGGGGG - GGGCATTTGITCACCTGGCCAGAGATCAGAGCAGGCTAA 11050 11060 11070 11080 11080 1100 11100 11100 11110	GG-ACT-CTGGATCCTGTCCASCTTTGAGACCCTACAGASCCATGTTCTCCTAGCACGTATCCCGGTCACTGTTCTTACCTTATTCCAGGGCTTTCACCTCAGCTTGCC 11170 11183 1119C 11209 11210 11220 11230 11240 11280 11280 11280	GGC ISSASCCAAGGSCAACGCAGCCGC-CTTGTTC GCSATGGTAGCTTCCCAGGACGCGCGCGCGCGCGCGCTG-CCCATCCTGTTTGCTACCTCCTAAAGCCAAAGGC 112-3 11300 11310 11320 11330 11340 11350 11350 11360 11370 11380 11380 11400	TGGCGGG-C-GG-CCTTCTAAAGTCGCGAAGGTTAGAAGGTTCCGGAAGGAACGGCGTGAGGAAGGA

FTG. 7

SCICCTISAGAACTCGGGAAGGAAGCAGGTCICIGAAGAAATACTICAGSAGTAGAAAGAGGAAGCTAGAGGGTTAAAATGCACTACACAGGAAAGGAATTTTCTTAGAGTTA From 11530 for 11540 for 11550 for 11560 for 11570 for 11580 for 11600 for 11610 for 11620 for 11630 for 11640	FACCGCCACGTAGGGAAGGAATGAAAACCTTTGAATATTAGTGAAAAAAGGGAAACTSCAACGCCTGTATTACT 1890 11700 11710 11720 11730 11740 11750 11760	
TAGA	FACCGCCACGTAGGGAAGGAATGAAACCTTTGAATATTAGTGAAAAAGGGAAACTSCAACGCCTGTATTACT 1890 11700 11710 11720 11730 11740 11750 11760	ی
11C1 30	60CT 50	AGCT
6111 116	CAAC 112	1666
ATGA	AC TS	ACCC
46AA	66 A A .	CATG
SAAC	A A A G	1600
10 (5 A A A S	A D D
116/	117.	GGAT
16CA(ATAT	5111(
600	175A	116
11	. T. 231	TAAT
AGAG	. A A 4 6	16671
1159	1171	TAR
3 5 A 5	A A G	1110
530	700	11650
16 T AC	. A C G 1	CATTI
15 94 3 70 07))))) () () ()
1157	ATA(AAC
BATA	1150)5 a A
A A G A S 6 0	TG4A 680	5 a a a
10 TG	67.01	1114
66TC 9	ACAA 9	् ष ७
6CA6 1155	TABA 1167	BCC S
.56A.	AAAC	CAA2.
540 540	GTGTAGTAAACTAAAACAAGTCTTGAATTGCAT 11003 11679 11089 11	1094
.TC 66	11 11	כ א א כ.
64 A C	T 2 5 2	TCAI
.TTSA 1153	41GTCT/ 11650	6011
SCICCTISAGAACTC GGGAAAGGAAGCAGGGTCTC TGAAGAAATACT	GTATETGTCTESAGGTGTAGTAAACTAAAECAAGTCTTGAATTGCAT 11659 11003 11679 11689	esa tacc titc a ica acaccica a recorrance a some some caccocatitics citte a actites tites a toccatecce toccate

FIG. 7k

		•				FIG. 8(a)
			· · · · · · · · · · · · · · · · · · ·	· - · ·		
-	1	0.000		ECOR1		GAATTC
	3 Ġ 🔞	0.002		HINF1		GAATC
	33	0.003		MB011	•	TCTTC
· 1. 1		0.004		ALU1	**	AGCT
	48	0.004		DDE1	*	CTGAG
	50	0.004	6	MNL1		GAGG
		0.007		MNL1	1	CCTC
		800.0	f	MST1		TGCGCA.
	95	0.008	i.	MHA1	ŭ	GCGC
1	12	0.009		MB01		GATC
1 :	20	0.010	ŧ.	98V1	•	GCAGC
1	20	0.010		FNU4H1		GCAGC
	23 🛴	0.010	•	BBV1		GCAGC
	23	0.010		FNU4H1		GCAGC
	3 4	0.011	•	00E1		CTGAG
	48	0.012		HPH1	•	GGTGA
	73	0.014		MNL1		GAGG
	PI	0.016		DDE1		CTTAG
	04 .	0.017		HINF1		GAATC
	47	0.021	•	SPH1	•	GCATGC AGCT
	65	0.022	•	ALU1		GCTGC
	66	0.022		88V1		GCTGC
	66	0.022		FNU4H1		GAACACTTTC
	05	0.026	,	XMN1 ALU1		AGCT
	76	0.032		MNL1	•	GAGG
	17	0.035	•	STU1		AGGCCT
	25	0.036	•	HAE111		GGCC
	9.5	0.036		RSA1		GTAC
	05	0.037		0051		CTTAG
	8 6 1 7	0.043	•	ALU1	÷	AGCT
		0.044		ALU1		AGCT
)	23	. 0 • 0 • •			`)	
	5 9	0.047		MNL1	ě	CCTC
	7 8	0.049		RSA1		GTAC
	90	0.050	•	DDE1	1	CTAAG
	21	0.052		ALU1	•	AGCT
	52	0.055		HINF1		GATTC
	32	0.062		HIND111		AAGCTT
	33	0.062		ALU1		AGCT
	81	0.066		MB011		GAAGA
	88	0.066		MNL1	•	GAGG
	16	0.069		MNL1		GAGG
•	•			•		

	• • •		. }			FIG. 8(b)	
	- 4	•					
818	0.0	59		FOK1		GGATG	
898		2	ရ	MNL1		CCTC	
898			, v [‡]	MST11	•	CCTCAGG	
899			· (;	DDE1		CTCAG	
913			Ş	DDE1	•	CTGAG	
929			Š.	HPH1		GGTGA	
976	0.08	32 🕟 🖫		TAQ1		TCGA	
1027	0.09	36		RSA1		GTAC	
1032	0.08	37		MNL1	. •	GAGG	
1054	0.09	39		MNL1		CCTC	
1072		* .	÷	HIND111		AAGCTT	
1073				ALU1		AGCT	,
1099			•	BBV1		GCAGC	
1099		•		FNU4H1		GCAGC	• .
1101			•	ALU1		AGCT	
1138			•	MNL1		GAGG	
1145			,	HINC11	•	GTTGAC .	
1150	0.09		•	FOK1		CATCC	
1161			•	ALU1		AGCT	
1167				HPH1		TCACC	
1193				HPH1		GGTGA	
1198				ALU1		AGCT	
1200				DDE1	;	CTG-AG	
1204		• -		MB011		GAAGA	
1226				MNL1	:	GAGG	•
- 1284-			•	DDE1	•	CTGAG	
1286				MNL1		GAGG	
1323	0.11		•	RS41	•	GTAC	
1365	0.11	•		BBV1		GCTGC	
1365	0.11			FNU4H1		GCTGC	
1370	0.11			XBA1		TCTAGA	
1424	0.12	-	•	DDE1		CTAAG	
1,427	0.12			ALU1	•	AGCT	•
1449				RSA1		GTAC	
1603	0.13			ALU1		AGCT	
1626	0.13			ACC1		GTATAC	
14.633		•		HINC11		GTTAAC	
TA 10:			PT	POTENTAL T	•	FAGE	
	1670 1672	10.7147 0.141		MNLT HAE1	11	GGCC	
*	1685	0.141		FOK 1		GGAT	
	1759	0.142		HINF1	1	GATT	
. %	1766	0.148		MNL1	•	GAGG	
**	1841	0.155	•	SAU96	5.1°	GGGC	
	1842	0.155		HAE11		GGCC	
	1076			MAGI	• • .	3000	

		· ·	FIG. 8(c)
1855 0.156	DDE1		CTTAG
1884 0.159	MB011	•	TCTTC
1901 0.160	AVA11		GGACC
1901 0.160	SAU961		GGACC
1939 0.163	MNL1		CCTC
1940 0.163	0051	·	<u>CTCAG</u>

1947	0.164	_ ALU1	AGCT
1965	0.165	HAE111	GGCC
1965	0.165	SAU961	GGCCC
203C	01171	RSA1	GTAC
2081	0 175	RSA1	GTAC
2097	0.177	HGA1	GACGC
21.0	0.178	4 LU1	AG C T
2112	0.178	55E1	CTCAG
2116	G.178	RSA1	GTAC
21 2 8	0.179	MB01	GATC
2141	0.180	MNL1	CCTC
2147	0.131	MNL1	CCTC
2150	0.181	FOK1	CATCC
2158	0.132	MNL1	CCTC
2161	0.182	MNL1	CCTC
2165	0.182	MNL1	CCTC
2171	0.183	ACC1	GTAGAC
2174	0.183	HINF1	GACTC
2222	0.187	DDE1	CTTAG
2225	0.187	ALU1	AGCT
2248	0.189	PST1	CTGCAG
2282	0.192	MST11	CCTAAGG
2283	0.192	DDE1	CTAAG
2287	0.193	FOKT	GGATG
2296	0.193	MNL1	CCTC
2301	0.194	ALU1	AGCT
2349	0.198	98V1	GCTGC
2349	0.198	FNU4H1	GCTGC
2422	0.204	HINF1	GATTC
2468	0.208	HINF1	GATTC
2483	0.209	9STE11	GGTAACC
2503	0.211	ALU1	AGCT
2524	0.212	XBA1	TCTAGA
2534	0.213	DOE1	CTAAG
			•

	•			FIG. 8(d)
2658	0.224	RSA1	•	GTAC
2678	0.225	SFNA1		GCATC
2726	0.230	HINF1	•	GAGTC
2728		HINC11		GTCAAC
2770_		HINF1	*	GATTC
2807	0.236	HGA1		GACGC
2811	0.237	DDE1		CTTAG
2965	0.250	HINF1	•	GATTC
2984	0.251	AV411	•	GGTCC
2984	0.251	SAU961		GGTCC
3012	0.254	MNL1		GAGG
3024	0.255	HINF1		GATTC
3032	0.255	ALU1	•	AGCT
3048	0.257	NDE1		CATATG
3090	0.260	MNL1		GAGG
3093	0.260	48011	*	GAAGA
7 06	0.262	RSA1		GTAC
3141	0.264	TAQ1		TCGA
3168	0.267	RSA1		GTAC
3193	0.269	MBO1		GATC
3213	0.271	HGIA1	•	GTGCTC
3216	0.271	0051		CTCAG
3220	0.271	MB011		GAAGA
3234	0.272	RSA1		GTAC
3263	0.275	. MNL1	•	GAGG
3333	0.231	NDE1		CATATG "
3412	0.287	BCL1	•	· TGATCA
٠.	• •			

3413	0.287	MB01	GATC
3415	0.288	HPH1	TCACC
3457	0.291	· DDE1	CTAAG
3462	0.292	HINF1	GACTC
3489	0.294	TAQ1	TCGA
3522	0.297	ECOR5	GATATC .
3585	0.302	RSA1	GTAC
→ 3624	0.305	BGL11	AGATCT
36 2 5	0.305	MBO1	GATC
3638	0.306	MB 01	GATC
3689	0.311	HPH1	TCACC
3792	0.319	ALU1	AGCT V

	•	υ	FIG. 8(e)
397	0.324	RSA1	GTAC
3905	0.329	oRS41	GTAC
3970	0.334	BSTN1	CCAGG
3970	0.334	SCRF1	CCAGG
3979		BSTE11	GGTAACC
4016	0.338	MNL1	GAGG
4018	0.339	SFNA1	GCATC .
4022	0.339	MB011	TCTTC
4368	0.368	HINF1	GAGTC
4384	0.369	RSA1	GTAC
4410	0.371	SFNA1	GATGC
4469	0.376	SFNA1	" GATGL
4520	0.381	RSA1	GTAC
4523	0.381	DDE1	CTGAG
4525	0.381	MNL1	GAGG
4529	0.381	ECOR5	GATATC
4533	0.382	TAG1	TCGA
4058	0.392	· HINF1	GAATC
4695	0.395	· ALU1	AGCT
4719	0.397	X8A1	TCTAGA
4727	0.398	SFNA1	GCATC
4769	0.402	ECOR1	GAATTC
4769	0.402	XMN1	GAATTCTTTC
4778	0.402	DDE1	CTGAG
4780	0.403	HINF1	GAGTC
4848	0.408	NDE1	CATATG
4961	0.418	HINF1	GATTC
4988	0.420	DDE1	CTGAG
5020	0.423	ALU1	AGCT
5022	0.423	DDE1	CTGAG GATTC
5049	0.425	HINF1	CCGG
5053	0.426	HP411	TGATCA
5085	0.428	3CL1	GATC
.5086	0.428	MB01	CAGCTG
→ 5157	0.434	PVU11	AGCT
5158	0.434	ALU1	GTAGAC
5225	0.440	ACC1	CTGCAG
5258	0.443	PST1	GAGG
5285	0.445	MNL1	GATATC
5339	0.450	ECOR5 RSA1	GTAC
5355	0.451	HGIA1	GTGCAC
53,67	0.452	RSA1	GTAC
5394	0.454 0.455	DDE1	CTCAG
5402	0.455	, BSTN1	CCAGG
5414	Ų • 43 0	, JJ 1141	

FIG.	81	(f)
110.	•	

	\$	•
5414 0.456	SCRF1	CCAGG
5421 0.456	MB011	GAAGA
	, MB01	GATC
-	ALU1	AGCT
5455 0.459	7601	
•	•	
,	***	•
•		:
5/24 0 /42	FNU4H1	GCGGC
5481 0.462	MNL1	GAGC
5490 0.462	ALU1	AGCT
5560 0.468	DDE1	CTGAG
5562 0.468	XMN1	GAAAGTATTC
5627 0.474	FOK1	GGATG
5653 0.476	HINF1	GAGTC
5657 0.476	PST1	CTGCAG
5672 0.478		GCAGC
5674 0.478	BBV1	GCAGC
5674 0.478	FNU4H1	CCTGG
5754 0.485	BSTN1	
5754 0.485	SCRF1	CCTGG
5761 0.485	SAU961	GGGCC
5762 0.485	HAE111	GGCC
5764 0.485	BSTN1	CCAGG
5764 0.485	SCRF1	CCAGG
5779 0.487	MNL1	CCTC
5813 0.490	ECOR5	GATATC
5621 0.490	HAE111	GGCC
5844 0.492	98V1	GCTGC
5844 0.492	FNU4H1	GCTGC
5845 0.492	PST1	CTGCAG
5863 0.494	BAL1	TGGCCA
5864 0.494	HAE111	, GG C C
5875 0.495	SAU961	GGGCC
5876 0.495	HAE111	GGCC
5886 0.496	SAL1	TGGCCA
5887 0.496	HAE111	GGCC
5898 0.497	MNL1	GAGG
5899 0.497	STU1	AGGCCT
5900 0.497	HAE111	GGCC
5922 0.499	ALU1	AGCT
5952 0.501	48011	GAAGA
5955 0.501	HINF1	GAATC
5961 0.502	20E1	CTAAG
	SAU961	GGGCC
5971 0.503	340701	

7		
1	FIG.	210
	LIG	U(K)

	• •		4
5972	0.503	HAE111	GGCC
-	0.504	MB 011	TCTTC
5987	0.505	BSTN1	CCTGG
5994		SCRF1	CCTGG
5994	0.505	48011	TCTTC
6000	0.505	ALU1	AGCT
6021	0.507	ACC1	GTCTAC
6026	0.507	•	GAGG
6037	0.503	MNL1	AGCT
6121	0.515	ALU1	TCTTC
6139	0.517	MB011	1
6177	0.520	MNL1	CCTC
6211	0.523	0051	CTTAG
6214	0.523	ALU1	AGCT
6233	0.525	HAE111	GGCC
-6248	0.526	· HIND111	AAGCTT
6249	0.526	ALU1.	AGCT
6275	0.528	AVA11	GGTCC
6275	0.528	SAU961	GGTCC
6305	0.531	rsa1	GTAC
6361	0.536	MB011	TCTTC
6370	0.537	BBV1	GCAGC
6379	0.537	FNU4H1	GCAGC
→ 6380	0.537	PVU11	CAGCTG
6381	0.537	ALU1	AGCT
6558	0.552	AVA11	GGTCC
	•		

		5 4 4 0 4 4	GGTCC
6558	0.552	SAU961	
6561	0.553	BSTN1	CCTGG
6561	0.553	SCRF1	CCTGG
6564	0.553	HPH1	GGTGA
6629	0.558	HINF1	GAATC
6639	0.559	MBO1	GATC
6674	0.562	HINF1	GAATC
	• • • •	XBA1	TCTAGA
6677	0.562	- :	AGGCCT
6683	0.563	STU1	7
6684	0.563	· HAE111	GGCC
6722	0.566	3BV1	₹ GCAGC
6722	0.566	FNU4H1	GCAGC
	0.570	SFNA1	GCATC
6767			GGATG
6793	0.572	FOK1	- · · · · · · · · · · · · · · · · · · ·
6848	0.577	HINF1	GACTC

FIG. 8(h)

- 			
6874	0.579	HINF1	GATTC
6911	0.582	ECOR1	GAATTC
6916	0.582	HPA11	CCGG
6984	0.588	ALU1	AGCT
6991	0.589	HINF1	GACTC
7028	0.592	SAU961	GGGCC
7029	0.592	HAE111	GGCC
7038	0.593	DDE1	CTCAG
7052	0.594	FOK1	GGATG
	0.594	S AU 961	GGGCC
7056		HAE111	GGCC
7057	0.594	MNL1	CCTC
7059	0.594	MB011	TCTTC
7124	0.600	A.	GAAGA
7155	0.603	MB011	GAAGAGTTY
7155	0.603	XMN1	CTAAG
7179	0.605	DDE1	AGCT
7182	0.605	4 L U 1	
7185	0.605	. HPH1	TCACC
7194	0.606	DDE1	CTGAG
719 ć	0.606	MNL1	GAGG
7237	0.609	ALU1	AGCT
7293	0.614	AVA1	CTCGGG
731 C	0616	MB011 ,	GAAGA
7313	0.616	SFNA1	GATGC
7322	0.617	ESTN1	CCAGG
7322	0.617	SCRF1	CCAGG
7343	0.618	RSA1	GTAC
7373	0.621	HGIA1	GAGCTC
7373	0.621	SAC1	GAGCTC
7374	0.621	· ALU1	AGCT
7376	0.021	DDE1	CTCAG
≻7378	0.621	PVU11	CAGCTG
7379	0.621	ALU1	AGCT
7394	0.623	HAE111	3G C C
7396	0.623	= BSTN1	CCAGG
7396	0.623	SCRF1	CCAGG
7408	0.624	DDE1	CTGAG
7410	0.624	MNL 1	GAGG
7438	0.626	FOK1	GGATG
7485	0.630	STU1	AGGCCT
7480	0.630	HAE111	GGCC
7488		MNL1	CCTC
7507	0.632	нрн1	GGTGA
7516	0.633	MNL1	GAGG
u u	0.634	ALU1	AGCT
*		MRO11	GAAGA
7547	0.636	MAUII	GAAGA

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			•
7580	0.638	HINF1	GATTC
7599	0.040	HINC11	GTCAAC
7619	0.642	MB011	GAAGA
7634	0.643	RSA1	GTAC
7637	0.643	DDE1	CTCAG
7659	0.645	ALU1	AGCT
7681	0.647	нрн1	GGTGA
7705	0.649	DDE1	CTAAG
7745	0.652	HINF1	GACTC
7753	0.553	MNL1	GAGG
7802	0.657	HINF1	GAGTC
7809	0.658	MB01	GATC
794G	0.669	BSTN1	CCTGG
794G	0.669	SCRF1	CCTGG
7963	0.671	MNL1	CCTC
7989	0.673	ALU1	AGCT
8002	0.674	HINF1	GACTC
3013	0.675	HGIA1	GTGCTC
8021	0.675	ALU1	AGCT
8031	0.676	MNL1	GAGG
8035	0.677	DDE1	CTGAG
8037	0.577	MNL1	GAGG
8046	0.678	HINF1	GAATC
8049	0.678	HPH1	TCACC
8053	0.678	. DDE1	CTGAG
3058	0.679	BSTN1	CCTGG
8058	0.679	SCRF1	CCTGG
8067	0.579	TAQ1	TCGA
8069	0.680	MNL1	GAGG
.80 7 2	0.680	88V1	GCTGC
8072	0.680	FNU4H1	GCTGC
3073	0.680	PST1	CTGCAG
8086	0.681	BCL1	TGATCA
8087	0.681	MBO1	GATC
3109	0.683	3DE1	CTGAG
8160	0.687	- HAE111	GGCC
816C	0.687	SAU961	GGCCC
8190	0.690	HPA11	CCGG
J •			•

F	ΙG	_	8	(i)
•		•	_	•	J	,

8190	0.690	NCI1	CCGGG	
8190		SCRF1	CCGGG	
8220	0.692	RSA1	GTAC	
8233	0.693	AVA1	CCCGGG	
8233	0.693	NCI1	CCCGG	
18233	0.693	SCRF1	CCCGG	
8233	0.693	SMA1	CCCGGG	
3234	0.693	HPA11	CCGG	
8234	0.693		CCGGG	
8234	0.693	SCRF1	CCGGG	
8238	0.694	HGIA1	GTGCTC	
8243	0.694	PST1	CTGCAG	
8282	0.697	NDE1	CATATG	
8357	0.704	DDE1	CTTAG	
8366	0.705	PVU11	CAGCTG	
8367	0.705	ALU1	AGCT	
8376	0.705	0051	CTAAG	
8382	0.706	HINF1	GATTC	
8396	0.707	MB011	GAAGA	
841G	0.708	MNL1	CCTC	
8417	0.709	HAE111	GGCC	
3417	0.709	SAU961	GGCCC	
8423	0.709	MNL1		(i,
3 T L 3		· · · · · · · · · · · · · · · · · · ·	•	
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		•	
8428	0710	BSTN1	CCAGG
8428	0.710	SCRF1	CCAGG
8440	0.711	BSTN1	.CCAGG
8440	0.711	SCRF1	CCAGG
3443	0.711	FOK1	GGATG
3447	0.711	AVA11	GGTCC
8447	0.711	SAU961	GGTCC
8477	0.714	BSTE11	GGTAACC
8492	0.715	NDE1	CATATG
3643	0.728	PST1	CTGCAG
9221	0.777	MB01	GATC
9263	0.780	MNL1	CCTC
9266	0.780	MNL1	· CCTC
9294	0.783	MNL1	GAGG
9335	0.786	FOK1	CATCC
9350	0.787	MB011	TCTTC
			•

FIG. 8(k)

9353	0.788		MB011		TCTTC	
9394	0.791		BSTN1	;	CCTGG	1
9394	0.791	•	SCRF1	•	CCTGG	
9400		*	MNL1		CCTC	
95 5 C	0.804		MB01	4	GATC	
9571	0.804		MB011		TCTTC	
9600		•	HGIA1		GTGCTC	•
9603		•	DDE1		CTCAG	
→ 9614			SAMH1	• , •	GGATCC	
9615	0.810	•	MB01		GATC	•
9626	0.811		BSTN1		CCAGG	
9626	0.811		SCRF1	•	CCAGG	
9641	0.812		ALU1		AGCT	
9643	0.812		DDE1		CTAAG '	
9647	0.812		MB011		GAAGA	
9676		13 ¹ 3	HINF1		GATTC	
9681	0.816		MB01		GATC	
- 9694	0.816		FOK1		CATCC	٠,
9697	,		BSTN1	•	CCTGG	
9697	0.317		SCRF1		CCTGG	
9723			MB011	•	TCTTC	
9747		•	NCI1		CCCGG	
9747		•	SCRF1		CCCGG	
	0.821		HPA11.	•	CCGG	
9762			HAE11		GGCGCC	
9762		2	NAR1		GGCGCC	
9763		ь.	HHA1		GCGC	
9777		•	ALU1		AGCT	
9787	0.824	•	MNL1) 	GAGG	
9791	0.825	,	DDE1		CTGAG	
9793	0.825	. •	MNL1	*	GAGG	
39814	0.826		HPA11	i r	cces	
9814	0.826	•	NCI1	į	CCGGG	
39814	0.826		SCRF1	· · · · · · · · · · · · ·	CCGGG	
9819	0.827	•	MNL1		GAGG	
9826	0.828		ALU1	1	AGCT	
9843	0.829		MBO1	<u>i</u>	GATC	
9864	0.831	. *	BSTN1		CCTGG	
9864	0.831		SCRF1		CCTGG	
9881	0.832		HINF1	• • • • • • • • • • • • • • • • • • • •	GACTC	•
10246	(*	3y	HINF1	4	GATTC	
10279			ALU1		AGCT	•
10281	0.866		0DE1		CTGAG	
10284	0.866		ALU1	1	AGCT	
10310	0 868	÷	TTH1111	ate s	GACCCTO	> TC

FIG. 8(L)

		•		
	10336	0.870	MNL1	CCTC
	10347	0.371	MNL1	CCTC
,	10351	0.872	FOK1	CATCC
	10455	0.880	HINF1	GAATC
	10463	0.881		CCTC
	10473	0.882	FOK1	GGATG
	10477	0.882	SAU961	GGGCC
	10478	0.332	HAE111	GGCC
	10482	0.883	ALU1	AGCT
	10505	0.885	PST1	CTGCAG
	10512	0.885	MNL1	GAGG
	10536	0.387	M301	GATC
	10543	0.888	PST1	CTGCAG
	10545	0.888.0	B3V1	GCAGC
	10545	J.888.	FNU4H1	GCAGC
	10563	0.390	0051	CTAAG
	10568	0.870	SFNA1	GCATC
	10589	0.392	PVU11	CAGCTG
	10590	0.892	ALU1	AG C T
	10605	0.393	HPH1	GGTGA
	10625	0.895	ALU1	AGCT
	10656	0.397	HPH1	TCACC
	10685	0.900	SFNA1	GATGC
	10093	0.901	M3011	TCTTC
	10733	0.904	BSTN1	CCAGG
	10733	0.904	SCRF1	CCAGG
	10751	0.905	ecl1	TGATCA
	10752	0.905	M501	GATC
	10760	0.906	HPH1	GGTGA
	10763	0.906	MB011	GAAGA
	10779	0.908	M5011	GAAGA
	10865	0.915	нрч1	GGTGA
	10869	0.915	ALU1	AGCT
	10699	0.918	MB011	GAAGA
	10925	0.920	HPH1	GGTGA
	1095G	0.922	HINF1	GATTC
	10958	0.923	MNL1	CCTC
	11015	0.928	93V1	GCAGÇ

FIG. 8(m)

	· •			
-11015-	0-928	FNU4H1	¥	GCAGC
11061	0.932	HINC11		GTTGAC
11073	0.933	ALU1		AGCT
-	0.934	FNU4H1	;	GCGGC
11095	, - · · · · · · · · · · · · · · · · · ·	HPH1	1 1 .	TCACC
11132	0.938			CCTGG
11135		3STN1		CCTGG
11135	0.938	SCRF1		•
11137	0.938	BAL1		TGGCCA
11138	0.938	· HAE111	•	GGCC
11145	0.939	MB01		GATC
·11157	0.940	DDE1		CTAAG
11170	0.941	SAMH1		GGATCC
11171	0.941	MBO1	• "	GATC
11181	0.942	ALU1	· .	AGCT
11256	0.948	BSTN1		CCAGG
11256	0.948	SCRF1	•	CCAGG
	0.949	нрн1		TCACC
11265		MNL1		CCTC
11268	0.949	DDE1	•	CTCAG
1126	0.949	•		AGCT
11272	0.949	ALU1	•	
11278	0.950	BSTN1		CCAGG
11278	0.950	SCRF1	•	CCAGG
11300	0.952	3 B V 1		GC A G C
٠		9		•

			•
1130G	0.952	FNU4H1	GCAGC
11303	0.952	FNU4H1	GCCGC
11314	0.953	NRU1	TCGCGA
1.1315	0.953	FNUD11	CGCG
11324	0.954	ALU1	AGCT
1133G	0.954	BSTN1	CCAGG
11330	0.954	SCRF1	CCAGG
11349	0.956	HPA11	CCGG
11356	0.956	HAE11	GGCGCT
11357	0.956	HHA1	GCGC
11367	0.957	FOK1	CATCC
11381	0.958	MNL1	CCTC
11428	0.962	FNUD11	CGCG
11429	0.963	HHA1	GCGC
11447	. •	HPA11	CCGG
11464	0.965	MNL1	GAGG
11404	0 0 70 3		

FIG. 8(n)

•				
11466	0.966		HAE111	GĠCŌ
11478	0.967	i	MNL1	GAGG
11481	0.967	•	RSA1	GTAC
11494	0.968		MNL1	CCTC .
11497	0.768	`.	BSTN1	CCAGG
11497	0.968	•	SCRF1	CCAGG
1150C	0.768		HAE111	GGCC
11500	0.968		SAU961	GGCCC
11504	0.969		FNUD11	CGCG
11505	0.969	,	HHA1	GCGC
11506	0.969		FNUD11	CGCG
11515	0.970		DDE1	CTCAG
1151)	0.970		HGIA1	GAGCTC
11519	0.970		SAC1	GAGCTC
11520	0.970		`ALU1	AGCT
11533	0.971		AVA1	CTCGGG
11557	0.973		MB011	GAAGA
11560	0.974		XMN1	GAAATACTTC
11581	0.975		MNL1	GAGG
11586	0.976		ALU1	AGCT
11591	0.976		MNL1	GAGG
11631	0.980	~ ·	DDE1	CTTAG
11648	0.981		X B 4 1	TCTAGA
11552	0.981	•	MNL1	GAGG
11701	0.985		MB011	GAAGA
11765	0.991		.ALU1	AGCT
11778	0.992		ALU1	AGCT
11828	0.996		HIND111	AAGCTT
11829	0.996		ALU1	AGCT
11845	0.998	•	BAMH1	GGATCC
11846	0.998		MB01	GATC
11868	0.999		PVU11	CAGCTG .
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Oligo N3 5' GATCCAGCTGA 3'
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Fig. 10

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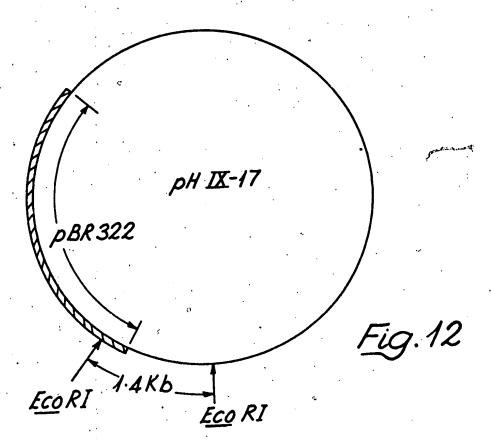
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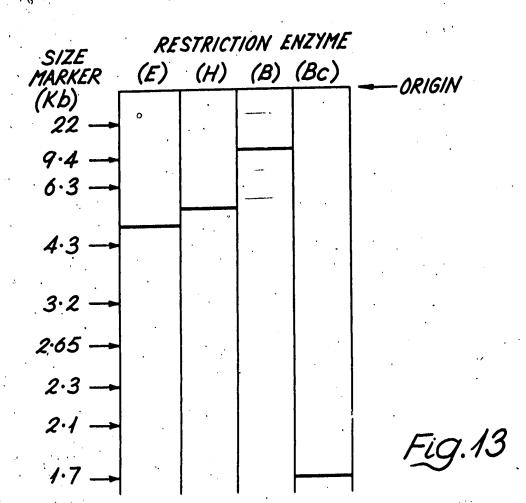
5' GAA TTCTCATGTT TGACAGCTTA TCATCGATAA GCTTCAGCTG GATCCTCTAC

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GCCGGACGCA 3'

Fig.11





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